Vitamin D
Breakfast of Champions

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Vitamin D Primer

- Majority vitamin D produced in the dermis (D3) UVB exposure
- Ability to manufacture vitamin D inversely proportional to skin pigmentation (SPF 8) and age
- Ability to manufacture vitamin D above 35° N limited
- Sun exposure can’t cause vitamin D toxicity
- Vitamin D is really a hormone, monokine not a vitamin
  - vitamin when it cannot be synthesized in sufficient quantities by an organism, and must be obtained from the diet.
- 1-25D crosses cell membrane and nuclear membrane to attach to VDRE in DNA
- Increases expression of > 200 genes
- 1-25D increases calcium absorption GI tract, mobilizes calcium from the skeleton (PTH)
- Decrease in vit D, increases PTH which increases production of 1-25 vitamin D
Vitamin D: Production and Metabolism

Skin

ProD₃ ⇔ PreD₃ ⇔ Vitamin D₃

Liver

25(OH)D

Kidney

PTH(+)  →  (+) low PO₄²⁻

Intestines

1,25(OH)₂D

Bone

Increase Calcium & Phosphorus Absorption

Mobilize Calcium Stores

Maintain Serum Calcium Phosphorus

Diet

Limited dietary sources of vitamin D:
- Fortified milk
- Fortified orange juice
- Salmon and other fatty fish
- Vitamin supplements

Adapted with permission from Holick MF. Curr Opin Endocrinol Diabetes. 2002;9:87–88.
Skin Color

- Evolutionary selection of skin color caused by the sun
- Evolved with loss of pelts to allow for heat dissipation, increased sun exposure darkened skin color
- Sun produces vitamin D (deficiency decreases fertility) but destroys folate (deficiency causes neural tube defects in pregnancy)
- 1.2 million years ago all skin was dark and remained so for the next 1.1 million years
- As humans moved out of tropics all the way to Arctic dark-skinned people could not produced vitamin D
- Estimate about 20,000 yrs to evolve dark to light skin
- Tanning evolved to protect humans from sun in summer, multiple genes control melanin production
Skin Color and Latitude

Dark skin Inuit people have high dietary vitamin D
Impact of Vitamin D Insufficiency on Skeletal Health

Vitamin D insufficiency is associated with\(^1\):
- Impaired calcium absorption
- Increased release of PTH
- Increased bone remodeling
- Bone loss leading to osteoporosis

In severe cases, deficiency results in more severe hyperparathyroidism, hypophosphatemia, proximal muscle weakness, bone pain and osteomalacia.

Why 400 IU?

- Index disease for vitamin D deficiency was rickets or osteomalacia.¹
- It is known that vitamin D prevents rickets.²
- Absence of rickets or osteomalacia was implicitly considered to be evidence of vitamin D sufficiency.¹
- 1919–1920: Rickets developed in dogs reared indoors and fed purified diets; preventable with cod-liver oil.³
- The recommended dietary allowance for vitamin D was set at 400 IU because that was the quantity in 1 teaspoon of cod-liver oil.²

Types of Vitamin D

**Vitamin D₂** (PERSCRPTION)
- Formed by irradiation of ergocalciferol, found in plants
- Provided by some dietary sources and multivitamins
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form
- D₂ is less potent than D₃

**Vitamin D₃** (OTC)
- Naturally occurring form in humans
- Formed by action of ultraviolet light on vitamin D precursors in skin
- Present in certain nutrients
- Biologically inert
- Conversion (OH) in liver and kidneys produces active form

Vitamin D: Biologic Functions

Vitamin D → 25(OH)D → 1,25(OH)₂D → Prostate Gland, Breast, Colon, Lung, Keratinocytes

1,25(OH)₂D → Regulation of Cell Growth and Differentiation (cancer prevention)

LIVER

KIDNEY

Calcium Homeostasis
Muscle Health
Bone Health

Blood Pressure
Regulation
Cardiovascular Health

Immunomodulation
(prevention of autoimmune diseases)

Vitamin D and Infection

Niels Ryberg Finsen
Awarded the Nobel Prize in Medicine and Physiology in 1903 "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated radiation, whereby he has opened a new avenue medical science for disease treatment

- Darby in 1776 used cod liver oil to treat TB
- Major cause of death in the rickets epidemics of the late 1800’s was TB
- Finsen lamp delivered 100IU vitamin D sq/cm = oral dose of 500,000IU
- Direct effect of UV light on bacterial killing
- Charpy in 1950 treated pulmonary TB with 1,200,000 IU qwk
- Streptomycin, INH 1957, vitamin D therapy remained an adjunct
- Liu 2006 vitamin D upregulated cathelicidin, an antimicrobial peptid which decreases mTB viability in macrophages

Liu et al, Science 2006
Higher 25(OH)D Levels Are Associated With Better Lower Extremity Function in Ambulatory Women

- 4,100 ambulatory adults included in NHANES III
- 60 to ≥90 years
- Functional measurements used to assess lower extremity function:
  - 8-ft walking speed test
  - Timed sit-to-stand test

LOWESS = locally weighted regression plot.

Reference range of 22.5–94.0 nmol/L (9.0–37.7 ng/mL).
N = 4,100; P<0.001.

Disorders Related to Vitamin D Deficiency

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Strength of Evidence</th>
</tr>
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<tbody>
<tr>
<td>Osteoporosis</td>
<td>++++</td>
</tr>
<tr>
<td>Falls</td>
<td>++++</td>
</tr>
<tr>
<td>Type 1 diabetes</td>
<td>++</td>
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<tr>
<td>Cancer</td>
<td>++++</td>
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<tr>
<td>Autoimmune diseases</td>
<td>++</td>
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<tr>
<td>Hypertension</td>
<td>+++</td>
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<tr>
<td>Periodontal disease</td>
<td>++++</td>
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<tr>
<td>Multiple Sclerosis</td>
<td>++</td>
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<tr>
<td>Susceptibility/poor response to infection</td>
<td>++++</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>++</td>
</tr>
</tbody>
</table>

*a+++++, strong evidence including one or more randomized trials; ++++, strong and consistent epidemiologic evidence, without, however, evidence from randomized trials; ++ and +, less strong evidence that is nevertheless suggestive.*

THE 25(OH)D CONTINUUM

modified after Heaney
**Institute of Medicine**  
**2011 Report on Vitamin D and Calcium Requirements**

- **RDA: IU/d (covers needs of >97.5%)**
  - **Ages** | **Serum Levels** | **Tolerable**  
  - 0-12m : 400IU | 20ng/ml | 1000-1500IU  
  - 1-70yr : 600IU | 20ng/ml | 2500-4000IU  
  - 71+yr : 800IU | 20ng/ml | 4000IU

- **Why 20ng/ml not 30ng/ml**
  - 20ng/ml supports maximal GI calcium absorption
  - PTH plateau ranges from 10-50ng/ml
  - 1% patients with osteomalacia with level >20ng/ml
  - Fracture incidence increased at levels < 20ng/ml

[www.iom.edu/vitamind](http://www.iom.edu/vitamind)
Causes of Vitamin D Deficiency

- **Reduced skin synthesis**
  - Sunscreen
  - Skin pigment
  - Aging
  - Season, latitude, time of day

- **Decreased bioavailability**
  - Malabsorption (GI, GI surgery)
  - Obesity

- **Increased catabolism**
  - Anticonvulsants, HAART, antirejection meds
  - Hyperthyroidism

- **Breast feeding**
  - Low vit D in milk
Causes of Vitamin D Deficiency

- Decreased synthesis 25OHD
  - Liver failure (>90%)
- Increased urinary loss
  - Nephrotic syndrome
- Decreased synthesis 1-25OHD
  - Kidney disease
- Acquired disorders
  - Primary hyperparathyroidism
  - Granulomatous diseases
Vitamin D Primer
Treatment

- 20 minutes sun, 5 minutes in tanning bed generated 5x’s vitamin D as 3.5oz salmon
- Vitamin D3 (cholecalciferol – animal based) more potent than vitamin D2 (ergocalciferol - plant based)
- Vitamin D2 50,000IU prescription
- Vitamin D3
  - 400, 1000, 2000, 5000, 50,000IU
  - In calcium supplements
Vitamin D and Sunlight

Skin Type Fitzpatrick scale
II always burns sometimes tans
V never burns always tans

UVB exposure 0.5 MED once weekly for 11 weeks
50% increase = 10ng/ml

Defining the Upper Limit of Vitamin D Intake

- Cases of vitamin D toxicity have been reported in patients receiving ≥10,000 IU/day for at least 1 month.
- No toxic effects were observed in individuals given 4,000 IU/day administered orally for 5 months.  

The End